CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-015

MEDICAL REVIEW

20

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MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT
NDA 19-537/S-015

Date submitted: 23 October 1991
Date received: 29 October 1991
Date assigned: 30 October 1991
Date completed: 9 February 1993

Applicant: Miles, Inc.
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Drug name: Generic: ciprofloxacin
Trade: Cipro

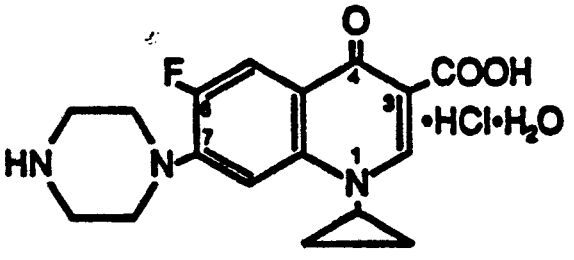
Class: fluroquinolone antimicrobial

Dosage form: Tablet

Route of administration: Oral

Chemical name: monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Structural formula:



Purpose of supplemental application: The purpose of this supplement is to demonstrate the safety and efficacy of ciprofloxacin in the treatment of mildly to moderately severe typhoid fever due to susceptible strains of *Salmonella typhi* and _____ at a dosage of 500 mg q12h for 10 days.

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INTRODUCTION

Background

Typhoid Fever.

Microbiology. Enteric fever is caused by the gram-negative organism *Salmonella typhi. S. paratyphi* (serotypes A, B, or C) causes a clinically related, but generally less severe, type of enteric fever termed paratyphoid fever. S. typhi, the far more important in terms of numbers of infections, is an aerobic, flagellated, glucose- and mannose-fermenting organism. It possesses three major antigenic determinants: the somatic, lipopolysaccharide (O) antigen; the flagellar protein (H) antigen; and the capsular (Vi) antigen, which is composed of N-acetyl galactosaminuronic acid. The Vi, or virulence, antigen is unique to the serotype *typhi*, and may be involved in protecting the organism from phagocytosis and/or intracellular destruction. Related Salmonellae, particularly *S. enteritidis* and *S. typhimurium*, also can cause an enteritis with mucosal invasion and bacteremia, but do not cause the complete syndrome of enteric fever.

Pathophysiology After ingestion, those organisms which remain viable after passage through the stomach attach to the apical microvilli of jejunal or ileal mucosal epithelium, in the vicinity of Peyer's patches. After replicating in intra-epithelial membrane-bound vacuoles, the organisms then gain entry to the intestinal lymph follicles and multiply within mononuclear cells. Organisms progress to the mesenteric lymph nodes where further multiplication occurs; they subsequently appear in the systemic circulation via the thoracic duct, disseminating to the bone marrow, spleen, biliary tree, and elsewhere. The severe abdominal pain characteristic of the disease, and for which the name enteric fever is given, is a result of inflammation of the ileum and mesenteric nodes. This intense inflammation can sometimes lead (in from 1-9 percent of cases) to intestinal perforation. The case-fatality rate is variable, ranging from less than 2 percent in developed nations to as high as 32 percent in developing nations in Asia, Africa, and the Far East (Hook, NEJM 310(2)116-118, 1984). The case-fatality rate is higher for elderly patients.

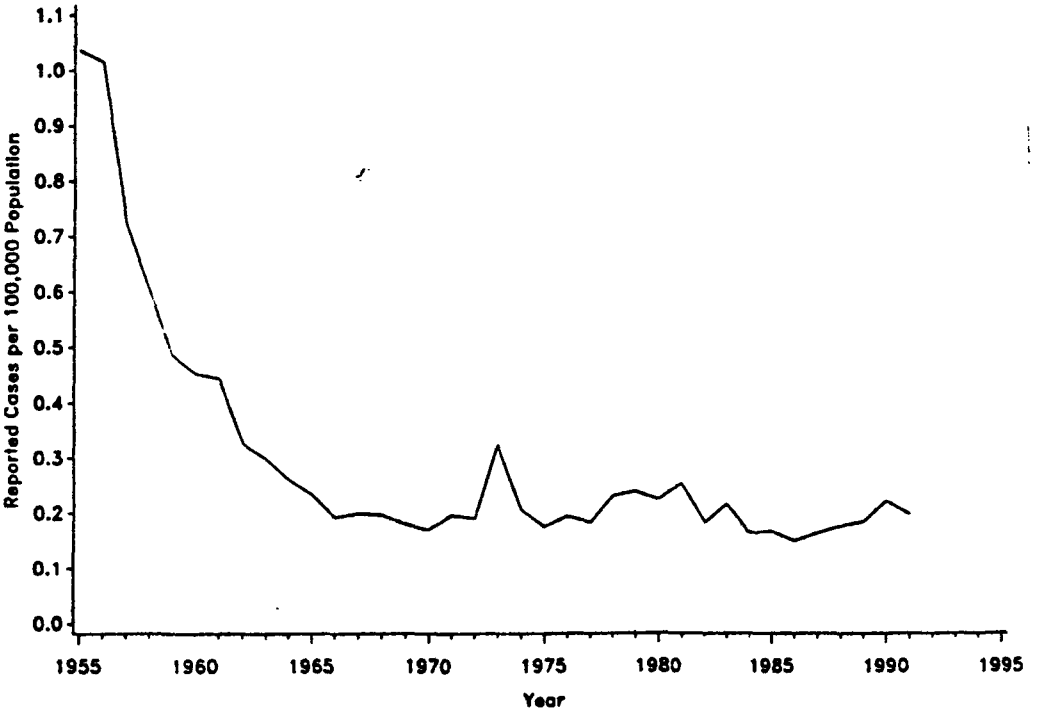
Epidemiology Man is the only known host for *S. typhi.* Spread of the organism is almost always via ingestion of food or water contaminated with excreta from a patient with typhoid or from an asymptomatic carrier.

In many countries, control of typhoid fever has been attained by improvement of living standards (readily obtainable clean water, adequate sewage treatment and disposal) which limit the fecal-oral spread of the organism from person to person. Despite these improvements, typhoid fever continues to be a major world health problem. Hundreds of thousands of cases occur annually in areas where economic, political, or sociocultural factors impede the development of

(or, in areas of civil turmoil, destroy) the infrastructure necessary to ensure adequate sanitation. An estimate of the worldwide annual incidence of typhoid fever was presented during a recent workshop sponsored by the Pan American Health Organization (Edelman R and Levine MM, Rev Inf Dis 8(3): 329-49, 1986): 6.98 million cases per year in south and east Asia; 749 thousand in west Asia; 4.36 million in Africa; 406 thousand in Latin America and the Pacific Islands; and 23,000 in the developed world. Worldwide, this adds up to an estimated 12.5 million cases annually (excluding China).

Approximately 20,000-40,000 cases of human *Salmonella* infections are reported annually in the United States. The overwhelming majority of these are non-typhoidal enterocolitis, usually involving various food products as vehicles of transmission. The annual incidence of typhoid fever in the United States is much lower, approximately 400-500 cases per year. (There were 456 cases reported in 1991, and there have been 199 cumulative 1992 cases tabulated in the MMWR as of the writing of this report.) As illustrated in the following CDC graph, the annual incidence per 100,000 population has remained fairly constant since the 1970's:

TYPHOID FEVER — By year, United States, 1955–1991



Surveillance data obtained by the CDC's Enteric Diseases Branch for 1990 (which are not identical to the data reported by the MMWR) included 571 isolates of *S. typhi*, 66 isolates of *S. paratyphi* A, and 87 isolates of *S. paratyphi* B.

Outbreaks in undeveloped countries are most frequently a reflection of the prevailing sanitary practices in the community, whereas sporadic outbreaks in more developed countries usually result from a combination of a lapse in usual sanitary practices and the simultaneous presence of an asymptomatic carrier. For example, a 1973 outbreak in Dade County, Florida, involving 230 persons in a camp for migrant farm workers, resulted from the failure of a water chlorinator while the water supply was simultaneously being contaminated by a typhoid carrier (Feldman RE et al, JID 130: 334-42, 1974). This was the largest outbreak of typhoid fever in the United States since 1939. (This single outbreak is responsible for the transient sharp increase in cases shown in the above graph for 1973.) The majority of typhoid fever cases in the United States (>66% of cases since 1975) are imported. Tourism in Mexico and India account for the majority of travel-related cases.

Prevention. Adequate sanitation and water treatment are the mainstays of prevention. Maintenance of typhoid in a community is due to the development of the chronic carrier state, defined as the asymptomatic passage of *Salmonella* organisms in the stool or urine for over one year. Such patients must be identified and treated. From 2 to 5 percent of typhoid patients may become chronic carriers, the rate being lower for young, otherwise healthy persons. Underlying biliary or urinary tract diseases, especially with stone formation, increase a patient's chances of becoming a chronic enteric or urinary carrier. These carriers may pass large numbers of Salmonellae in their stools or urine for many years. (One patient reported in the classic paper on treatment of typhoid carriers with ampicillin [Simon HJ and Miller RC, NEJM 274(15), 807-815, 1966] had documented fecal carriage for 27 years prior to enrollment in the study.) The organisms are known to reside in the biliary tract. Prior to the advent of antibiotic therapy, surgical cholecystectomy was the only reliable method of eradicating *S. typhi* carriage. In patients with urinary carriage of *S. typhi* and underlying urinary tract pathology secondary to *Schistosoma hematobium*, eradication of the urinary carrier state of *Salmonella* can be achieved by treatment of the schistosomiasis (Farid Z et al, J Trop Med Hyg 73: 153, 1970).

A vaccine for typhoid has been available for many years. Pfeiffer and Wright, in 1896, independently reported that a vaccine against typhoid fever could be prepared by heat-inactivating cultures of typhoid bacilli, then preserving them in phenol. Systematic use of this vaccine in the U.S. Army, starting in 1912, was followed by a diminution of approximately 90% in the incidence of typhoid fever. Controlled field trials of this vaccine, carried out by the WHO in the 1950s and

1960s, demonstrated that the heat-phenolized vaccine conferred a 50% to 75% protection against typhoid fever. This parenteral vaccine (and the similar, acetone-inactivated alternative) is somewhat notorious for its reactogenicity. In controlled studies, approximately 25% of recipients of either vaccine developed fever and malaise, leading to absenteeism from school or work in 15% of recipients. More recently, a live attenuated oral vaccine has been developed which is now available in the USA. Reported efficacy rates for various formulations of this vaccine range from 70% to 95% in different studies. This oral vaccine is much better tolerated by its recipients. A recent publication (Cruz SJ, Lancet 341: 49, 1993) claimed that, of 1,025,828 doses administered in the US, there have been 58 adverse event reports (0.0056%), predominantly abdominal cramping and discomfort.

Vaccination is an appropriate prevention strategy for travellers and military units entering an endemic area. Vaccination has also been used in large-scale typhoid control programs in hyperendemic populations. Nonetheless, despite continued vaccine improvements, the mainstay of prevention will continue to be identification and treatment of chronic carriers, in the setting of an adequate level of public health infrastructure.

Therapy. The era of antimicrobial therapy for typhoid fever began in 1948, when Woodward et al first described the efficacy of chloramphenicol (Woodward TE et al, Ann Int Med 29: 131, 1948). Chloramphenicol remains the drug of choice in areas of the world where resistance is not a problem, and is currently the only antimicrobial approved by the FDA for the treatment of typhoid fever in the United States. Sporadic cases of resistant isolates have been described in countries such as India, Greece, Israel, Spain, and Chile. A well-documented epidemic of chloramphenicol-resistant *S. typhi* occurred in Mexico in 1972, numbering in excess of 10,000 cases (Olarte G and Galindo E, Antimicrob Agents Chemother 4(6): 597, 1973).

Ampicillin and trimethoprim/sulfamethoxazole were developed in the 1960s, and both were reported to be effective therapy for typhoid fever (Kaye D et al, NEJM 269(20): 1084, 1963; Robertson RP et al, NEJM 278(4): 171, 1968; Akinkugbe OO et al, Br Med J 3: 721, 1968). Both had a toxicity advantage over chloramphenicol, insofar as the phenomenon of chloramphenicol-induced agranulocytosis had been well-described by that point in time. Furthermore, unlike chloramphenicol, ampicillin was reported to be effective in eradicating the chronic carrier state (Simon HJ and Miller RC, op.cit.).

Epidemic strains of multiply-resistant *S. typhi* have been described. The 1972 Mexico outbreak involved a strain which exhibited resistance to chloramphenicol, tetracycline, streptomycin, and sulfonamides (Olarte and Galindo, op. cit.). Resistance was found to be mediated by a single plasmid which could be experimentally transferred to *E. coli*. A second resistance type was isolated during this outbreak, which was additionally resistant to ampicillin and kanamycin. Since the 1970's, increasing prevalence of these resistance plasmids has been noted among *Salmonella* isolates from endemic areas. These multiresistant isolates are

occasionally responsible for cases of typhoid fever in more developed countries, such as Great Britain (Lohse AW and Rapoport M, Lancet ii: 1407, 1987) and Canada (Harnett N et al, Lancet ii: 177, 1992). A single, 80 kB plasmid has been found to code for the multiresistant phenotype. Third-generation cephalosporins such as cefotaxime, ceftriaxone, and cefoperazone have been used in the treatment of multiresistant *S. typhi* (see review by Soe GB and Overturf GD, Rev Inf Dis 9(4): 719, 1987), particularly in pediatric patients for whom the safety and effectiveness of fluroquinolones have not been established.

Ciprofloxacin.

Ciprofloxacin was approved by the FDA in 1987 for the following indications: lower respiratory infections, skin and skin structure infections, bone and joint infections, urinary tract infections, and infectious diarrhea. None of these indications included *Salmonella* as a designated microorganism, although *Salmonella spp.* was included in the **MICROBIOLOGY** *in vitro* activity subsection. The MIC_{90} for *S.typhi* is ≤0.097 µg of ciprofloxacin/mL. The bioavailability is approximately 60%, and peak concentrations in plasma average 2.4 µg/mL after a 500 mg oral dose. The elimination half-life is 3 to 4 hours in the setting of normal renal function.

Several pharmacodynamic characteristics of ciprofloxacin make it an appropriate drug to study in the therapy of typhoid fever. Ciprofloxacin penetrates tissues well (57% of the maximum serum concentration at 2.6 hours post administration, in a human blister fluid study [Crump B et al, AAC 24(5): 784-6, 1983]), and reportedly achieves bile concentrations as high as ten times the serum levels (Diridl G et al, Eur J Clin Micro 5(2): 260-1, 1986). Furthermore, ciprofloxacin has been shown to concentrate in human neutrophils. One study (Easmon CS and Crane JP, J Antimicrob Chemother 16: 67-73, 1985) found the gradient to be from 4 to 7 times that of the extracellular concentration. Another study (Traub W, Chemotherapy 30: 379-86, 1984) found that ciprofloxacin was bacteriocidal to intracellular *Serratia marcescens* with a potency equivalent to that of rifampin.

Early studies of ciprofloxacin's clinical utility included settings in which typhoid fever was endemic, such as an open study of 104 patients in Guatemala by Ramirez et al (AAC 28(1): 128, 1985). This study happened to include 38 patients who presented with *S. typhi* bacteremia and/or bone marrow infection. Of this subset of 38 patients, 36 were considered evaluable. Ciprofloxacin at a dose of 500 mg q12h was effective in eradicating 35 out of the 36 evaluable infections, although the duration of followup was not specified. Subsequently, further clinical studies were initiated to investigate the efficacy of ciprofloxacin in acute typhoid fever.

The efficacy of ciprofloxacin for eradication of the *S. typhi* chronic carrier state has been insufficiently studied. (NB: The sponsor is not seeking such an indication in this efficacy supplement.) One prospective study, done in Chile,

enrolled 12 chronic *S. typhi* carriers and treated them with 750 mg of ciprofloxacin for 28 days (Ferreccio C et al, J Inf Dis 157(6): 1235-9, 1988). Therapy was prematurely discontinued in two patients because of adverse reactions (urticarial skin rash in one, and decreased hemoglobin in another). Of the ten who completed therapy, one was a treatment failure (cultures reverted to positive three weeks following therapy) and one was reinfected with a different phage type of *S. typhi* six months following completion of therapy. In all, ten of twelve patients (including the two who had shortened courses of therapy due to adverse events) had documented eradication of carriage over a one year follow-up period. Further studies need to be completed to ascertain the true efficacy of ciprofloxacin in eradicating the chronic carrier state.

Proposed Labeling Changes.

Proposed labeling calls for the following changes:

"**Typhoid Fever** (enteric fever) caused by *Salmonella typhi* and ' ——— ——— to be added to the **INDICATIONS AND USAGE** section.

"*Salmonella typhi* and ——— to be added to the list of Gram-negative bacteria in the '...has been shown to be active against most strains of the following organisms in both *in vitro* and in clinical infections" portion of the **Microbiology** portion of the **CLINICAL PHARMACOLOGY** section.

In the **DOSAGE AND ADMINISTRATION** section, the statement "...for typhoid fever is 500 mg every 12 hours" has been added to the statement "The recommended adult dosage for infectious diarrhea is 500 mg every 12 hours." Also, an entry for "Typhoid Fever...Mild/Moderate...500 mg...q12h...1000 mg" has been added to the DOSAGE GUIDELINES table which is included in this section.

Contents of Supplement.

Supplement SEI-015 of NDA 19-537 contains the following:

1. Study #D84-052-02, entitled "A comparative, double-blind efficacy and safety study of ciprofloxacin with chloramphenicol in the treatment of typhoid fever." This study was performed at a single site in Mexico. It used a 750 mg bid dose of ciprofloxacin in 18 patients, compared to 750 mg chloramphenicol qid in 19 patients. (Volumes 8 and 9.)

2. Study #D87-054, entitled "A comparative, double-blind efficacy and safety study of ciprofloxacin with chloramphenicol in the treatment of typhoid fever." This study was performed at two sites, using a 500 mg bid dose of ciprofloxacin vs a 750 mg qid dose of chloramphenicol. There were 52 patients enrolled in each of the two arms at the Peru study site, and 60 patients enrolled in each of the two arms at the Guatemala study site. (Volumes 10 thru 16.)

3. Study # SN 866, entitled "A comparative study of ciprofloxacin with co-trimoxazole in the treatment of Salmonella enteric fever." This open-label, comparative, randomized study was performed at six different hospitals in the Philippines, in the context of a study of both oral and intravenous ciprofloxacin for a variety of infectious indications. Forty patients were enrolled, with 20 patients in each arm. Ciprofloxacin was dosed at 500 mg bid for 10 days, and co-trimoxazole was dosed at 160 mg trimethoprim/800 mg sulfamethoxazole bid for 14 days. Material submitted includes the study summary alone; no line listings or case report forms are submitted. (Volume 16)

4. Study #SN 332, entitled "Clinical evaluation of ciprofloxacin in the Philippines." This consists of a publication, taken from Excerpta Medica Asian Pacific Congress Series, No. 62, 1988, from the First Philippine Ciprofloxacin Symposium. Included in this publication are 20 patients with typhoid fever, who received ciprofloxacin at a dose of either 500 mg bid or 500 mg tid. Number of patients in each of these dosage regimens was not specified, and duration of therapy was anywhere from 7 to 14 days. No other material, aside from this single publication, is submitted with this study. (Volume 16)

5. Study #SN 9970, entitled "Ciprofloxacin in Salmonella infection and abdominal typhoid." This consists of a publication, in German (with translation), from the journal Dtsch Med Wschr 111: 1599-1602, 1986. This is a series of ten case reports, including three patients with 'abdominal typhoid'. Dosage was 500 mg bid for 3, 5, and 15 days. No other material is submitted. (Volume 16)

These studies will be presented in the same order in which they appear in the submitted material. However, by order of importance, Study D87-054 is the key portion of this submission. Each of the two study sites in Study D87-054 enrolled more patients than the total enrollment of Study D84-052. Given this, along with the geographic separation of the two sites in D87-054, and the fact that this was the study which used the dosage of ciprofloxacin for which the sponsor seeks approval, Study D87-054 can be considered as two separate, adequate, well-controlled studies. Study D84-052, with its smaller numbers, technical problems, and different dosage of ciprofloxacin, will be considered supportive only.

STUDY #D84-052-02: A comparative, double-blind efficacy and safety study of ciprofloxacin with chloramphenicol in the treatment of typhoid fever.

I. Study objective

To compare the effectiveness and safety of ciprofloxacin with that of chloramphenicol in the treatment of typhoid fever.

II. Study design

This was a prospective, double-blinded, randomized study of standard therapy (chloramphenicol) vs. ciprofloxacin. It was conducted at a single site in Guadalajara, Mexico from June 1985 to May 1987. Enrollment was open to adult men and women with clinical signs and symptoms of mild-to-moderate typhoid fever.

After being interviewed and examined, patients meeting enrollment criteria (see below) were invited to participate in the study. Informed consent was obtained, and baseline laboratory and culture specimens were collected (see **Clinical Observations and Laboratory Measurements**, below). Patients were randomized in blocks of six to either of the two treatment arms: chloramphenicol 750 mg po q6h or ciprofloxacin 750 mg po q12h

Comment:

The protocol states, "When feasible, the physical examination should be performed by the same study team member throughout the trial so that the severity scale for each sign and symptom will remain constant."

This reflects the subjective nature of such measures as a severity scale. Any claims of efficacy based on such measures will be interpreted accordingly.

Patients were hospitalized and observed daily. Vital signs were recorded every six hours. The duration of blinded therapy was for fourteen days or for seven days after the patient became afebrile (T < 100.0 F), whichever was longest. Drug supplied by the sponsor was in 21-day packets.

Comment:

There is no specific mention of whether the patients were in-patients throughout the medication period. It would seem logical that they were, if the temperature and vital sign data were to be efficiently collected.

No maximum duration of therapy was mentioned in the protocol.

III. Enrollment Criteria.

1. Male or female patients age 18 or greater.

Comment:

Ciprofloxacin is inappropriate for use in pregnant women, given its arthrotoxicity in the juvenille beagle dog model. Provision for pregnancy screening should have been included in the design of this protocol, and such patients should have been treated with chloramphenicol.

2. Signs and symptoms consistent with typhoid fever, including: fever, headache, anorexia, abdominal discomfort, cough, relative bradycardia, rose spots, abdominal tenderness and distention, and hepatosplenomegaly.

Comment:

No mention is made of how many of these diagnostic criteria were necessary for enrollment. Since there is a strict microbiologic requirement for evaluability (i.e., blood or bone marrow culture positive for S. typhi or S. paratyphi), the clinical criteria are not as crucial.

3. Prior antibacterial therapy is acceptable.

Comment:

The protocol makes no further clarification of this statement. Since patients who have failed prior therapy may be more difficult to treat successfully, it will be important to assure that such patients are evenly distributed between the two treatment arms.

IV. Exclusion Criteria.

1. Age less that 18 years.
2. Patients who are delirious, obtunded, stuporous, or comatose.

Comment:

These signs, along with hypotension, are regarded to be indicators of poor prognosis in typhoid fever. The protocol does not attempt to define "delirious", "obtunded", or "stuporous". One study (Hoffman SL et al, NEJM 310(2): 82-88, 1984) showed a significant benefit to high-dose intravenous corticosteroids in this group of patients. Since steroids were not specifically proscribed in the protocol, their use will be carefully monitored in this review. If a patient was judged a candidate for steroid therapy, then he was probably too ill to fit the 'mild to moderate' disease category and would therefore be ineligible for this protocol.

3. Patients with gross gastrointestinal bleeding.
4. Patients with peritonitis.
5. Patients with signs or symptoms indicative of meningitis.
6. History of allergy to any quinolone derivative including nalidixic acid, pipemidic acid, oxolinic acid, rosoxacin, or norfloxacin.
7. History of allergy to chloramphenicol or any of its derivatives.
8. Renal impairment (i.e., serum creatinine greater than 1.6 mg/dL).

V. Number of Patients.

A sufficient number of patients were to be enrolled to insure that 100 were suitable for evaluation of bacteriological response to the study drugs.

Comment:

No attempt is made to statistically justify this number of patients. Furthermore, the study was halted after enrolling 37 patients. No explanation is given for the premature termination of this study.

VI. Clinical Observations and Laboratory Measurements.

Clinical parameters measured included:

1. Demographic data and medication history.
2. Vital signs and physical examination parameters, with particular attention to the presence or absence of orthostatic hypotension, and the abdominal examination (distention, tenderness, and presence of bowel sounds).

Comment:

1. The protocol again states, "When feasible, the physical exam should be performed by the same study team member throughout the trial so that the severity scale for each sign and symptom will remain constant." However, no such 'severity scale' is included in the protocol.

2. Attachment 1 outlines the frequency with which clinical and laboratory measurements were performed during this study.

Microbiologic parameters included:

1. At least two blood cultures, one hour apart, prior to initiation of therapy. Blood cultures were also to be collected daily during the first week of therapy, as well as at any other time that was deemed clinically appropriate. Follow-up cultures were to be taken one day and two weeks post-therapy. Blood cultures were done on biphasic media, and identification was via API 20E and *Salmonella* typing sera.

Comment:

1. The protocol makes no mention of bone marrow culture, but several patients in this study had bone marrow samples taken during their diagnostic evaluation. Six chloramphenicol patients and eight ciprofloxacin patients were cultured in this manner. In two cases (patients 003 and 014, both chloramphenicol-treated), the bone marrow culture was the only positive specimen at the time therapy was started.

2. The precise method of bone marrow sampling used is not specified.

3. For the purposes of this review, only blood or bone marrow culture positivity will be accepted as confirming the diagnosis of typhoid fever.

2. Urine and stool were also cultured at the same time intervals as blood. These specimens were plated on MacConkey, SS, and Hektoen media (both directly, and after overnight enrichment using Selenite broth).
3. Serologic studies to be collected at entry were to include titers vs typhoid O antigen (the Widal test), and paratyphoid A & B; Brucella titer; and ASO titer. A reference serum sample was also collected for storage at -70°C.
4. Baseline stool and urine examinations for ova and parasites.

5. In patients presenting with cough, baseline and follow-up sputum cultures for bacteria, fungi, and AFB.
6. Susceptibilities of all clinical isolates were done using both standard modified Kirby-Bauer techniques, as well as serial tube dilutions in Mueller-Hinton broth. Zone sizes, using a 5 µg ciprofloxacin disc, were interpreted using the following criteria: Susceptible ≥18 mm; Intermediate 12-17 mm; and Resistant ≤11 mm. An organism with an MIC of ≤1 µg/mL by tube dilution assay was considered sensitive; MIC's of >1 but ≤2 µg/mL were considered intermediate. Sensitivity testing vs chloramphenicol was performed as outlined in the package insert.

Laboratory studies included:

1. Baseline CBC, blood chemistries, and urinalysis. These studies were repeated during the course of the study, as shown in Attachment 1.
2. Blood samples for assay of ciprofloxacin levels were to be collected 1-2 hours after the first daily dose, in selected patients.
3. Baseline EKG and chest X-ray.

VII. Premature Termination of Therapy

The following reasons for early termination of therapy were given in the submitted protocol:

1. Persistent fever or no improvement in symptoms after eight days of blinded therapy. These patients will be considered treatment failures.
2. Any patient who has a significant worsening of his condition after entering the study: development of an abnormal state of consciousness, gross gastrointestinal bleeding, signs of peritonitis, or signs of shock (defined as systolic BP < 90 mm Hg). These patients will be considered treatment failures and switched to IV chlor-amphenicol plus steroids, if typhoid is still the suspected etiology.
3. Any patient who develops a serious toxic or allergic reaction will be terminated from the study.
4. If superinfection develops, study drug should be discontinued and other appropriate therapy instituted.

Comment:

The protocol allows up to eight days of persistent fever before calling a patient a clinical failure. This is considerably longer than the five days proposed in the IDSA guidelines now under consideration. For the purposes of this review, patients will be considered clinical failures if they have persistent fever, or no improvement in symptoms, after five days of therapy.

VIII. Concomitant Therapy

VIII. Concomitant Therapy

The protocol does not expressly proscribe concomitant antimicrobial therapy; it states, "other antimicrobial agents should not be administered concomitantly unless they are required in the interest of the patient's management."

Comment:

Such cases will be considered individually, and will be deemed non-evaluable if the added antibiotic has activity against enterobacteriaceae.

IX. Follow-up

The protocol calls for re-evaluation of patients, with "appropriate" laboratory and diagnostic tests, at two weeks post-completion of therapy. Stool and urine specimens must then be obtained for follow-up culture.

Comment:

1. The following is excerpted from the IDSA Draft Guidelines for the Evaluation of a New Anti-Infective Agent for the Treatment of Typhoid Fever: "All sites from which S. typhi was recovered pre-therapy should be documented to be culture negative at the completion of therapy. Optimally, blood cultures should be documented as sterile, following completion of therapy (preferably 24 hours later); alternatively, a patient who appears clinically cured (afebrile, normal WBC count and differential) and from whom S. typhi has been eradicated from all other sites, may be considered to have presumptive microbiologic eradication if repeat blood cultures are not obtained. For patients with initial positive stool cultures for S. typhi, three negative stool cultures, spaced 3-7 days apart, is the recommended method for documenting eradication."

2. Two weeks of post-therapy follow-up is inadequate to document eradication of the chronic carrier state.

X. Adverse Event Monitoring

All patients were to be carefully evaluated for any adverse reactions which may have been potentially related to the study drugs. All such events were characterized as mild/moderate/severe, and were ascribed a relationship to study drug administration based on the temporal relationship of the event to the administration of the drug (highly probable, probable, possible, remote, or none).

XI. Evaluability

In order for an enrolled patient to be considered evaluable for efficacy, the following conditions were required by the protocol:

1. A history compatible with acute typhoid fever.

Comment:

Although a list of compatible signs and symptoms were given in the protocol, a well-defined set of clinical and/or historical findings which defined the presumptive diagnosis was not specified.

2. A culture of stool, urine, or blood positive for *S. typhi* or *S. paratyphi* within the 48 hours prior to treatment; *OR* a four-fold increase in agglutinin titer.

Comment:

An enrolled patient with nonspecific symptoms and a stool culture positive for S. typhi is not adequate, as this may be a chronic carrier with an unrelated, non-typhoidal illness. This reviewer will consider only those patients with blood (or bone marrow, or other non-gastrointestinal site) culture positive for S. typhi or S. paratyphi, as evaluable for efficacy.

A rise in agglutinin titer will not be considered adequate for the diagnosis of typhoid fever in this review. Other illnesses, especially infections with other gram-negative bacilli, may cause nonspecific elevations of agglutinins because of cross-reacting antigens (BMJ 1: 389, 1978); prior vaccination status may also affect these titers. For these reasons, such serologic tests are considered to have only an adjunctive role in the diagnosis of typhoid fever.

3. The isolate must be sensitive to the study drugs by disc diffusion or tube dilution assay.
4. Appropriate during-therapy and post-therapy cultures must be obtained.

Comment:

The term 'appropriate' is subjective. Differences exist between the sponsor and reviewer in the interpretation of what constitutes 'appropriate' cultures.

The inadequacy of post-therapy cultures was the major shortcoming of this study.

5. Lower respiratory tract infection must be confirmed by isolation of *S. typhi* or *S. paratyphi* from an adequate sputum specimen, and the pre-therapy chest X-ray must support the diagnosis of LRT infection. In such cases, a follow-up chest X-ray must be obtained to document clinical response. In the absence of any sputum production, follow-up sputum cultures will not be required.

Comment:

There were no such patients enrolled in this study.

6. The study drug must be given for at least 8 full days, except in cases of therapeutic failure.
7. "Appropriate cultures must have been obtained after the conclusion of drug treatment, except... if the procedure of obtaining a post-treatment culture is unduly invasive and not justified because of an obvious response of the infectious process."

Comment:

The above statement is a direct quotation from the protocol.

Patients cannot be classified as microbiologically eradicated if there is no post-therapy culture which documents eradication. However, if a patient is diagnosed by blood or bone marrow culture, and has a clear clinical response with documented clearance of blood cultures while on therapy, a post-therapy stool culture will be considered adequate to document presumptive eradication.

8. "No other appropriate antimicrobial should have been given along with the study drug."

Comment:

This curious wording, again quoted from the protocol, confirms what is stated in section VIII, above: that is, concomitant antimicrobials are not necessarily regarded by this protocol as a reason for non-evaluability. Cases in which other antimicrobials are used will be carefully reviewed; if that antimicrobial has known activity against Enterobacteriaceae, the patient will be considered non-evaluable or, if cultures remained positive for S. typhi when the additional coverage was started, a bacteriologic failure.

XII. Study Endpoints

A. Clinical Response

The protocol states that assessment of clinical response will be based on serial examinations of the patient. All pertinent laboratory tests or procedures which reflect the course of the disease will be used to assess the clinical response. The clinical response will be assessed by noting the time from initiation of therapy to: time to last febrile episode, last episode of nausea, last episode of abdominal pain, last episode of headache, last episode of anorexia, and last episode of coughing.

Comment:

1. The objectivity of these serial observations will be dependent upon their being performed in a blinded fashion.

2. The draft IDSA guidelines mention time to defervescence and time to normalization of WBC count as the two parameters most important to compare between the two regimens. The other clinical parameters mentioned (time to resolution of anorexia, etc.) will be considered to be of minor interest only.

At the completion of therapy, each patient's clinical response will be categorized as either complete resolution, improvement (either marked or slight), failure, or indeterminate.

B. Bacteriologic Response

The results of blood, urine, and stool cultures collected during the course of the study (i.e., before, during, and one day following completion of therapy) will be compiled, and the individual patient responses will be classified as follows:

- Eradication (early and complete), meaning the isolate was eradicated during therapy and remained eradicated at 24-hour follow-up
- Eradication (late and complete), meaning the isolate was present during therapy but no longer present at 24-hour follow-up
- Persistence, meaning the isolate was present both during therapy and at 24-hour follow-up
- Superinfection, meaning the presence of a new infecting organism (associated with signs and symptoms of infection) during therapy or at 24-hour follow-up
- Indeterminate response, meaning that the bacteriologic response cannot be determined (e.g., 24-hour post-therapy cultures not obtained)

Bacteriologic response at follow-up will be determined based on cultures obtained at the 2 week follow-up evaluation. These responses will be classified as follows:

- Eradication at follow-up, meaning the isolate was absent at the 2-week follow-up visit
- Eradication (early or late) with recurrence, meaning the isolate was absent during and/or immediately after therapy, but reappeared (associated with signs and symptoms of infection) at the 2-week follow-up
- Eradication (early or late) with reinfection, meaning the isolate was absent during and/or immediately after therapy, but a DIFFERENT isolate (again associated with signs and symptoms of infection) is cultured st the 2-week follow-up.

Comment:

1. The protocol requires collection of blood cultures one day AFTER completion of therapy. As will be seen, this was rarely accomplished.

2. The protocol also calls for 'cultures' to be obtained at the two week follow-up evaluation, in order to evaluate bacteriologic response. As will be seen, these cultures, if obtained at all, were poorly documented. Furthermore, the sites to be cultured were not specified.

3. If an isolate is once again cultured at 2-week follow-up, it will be considered a recurrence, regardless of symptomatology.

4. The protocol appropriately calls for the use of serotyping and comparison of antibiograms to determine recurrence vs reinfection. Once again, presence of signs/symptoms will be considered less important than the bacteriologic data.

C. Overall Response

The clinical and bacteriologic responses were combined by the investigator, and an overall assessment of the course of therapy was made. Each patient's outcome was characterized as 'completely successful', 'partially successful', 'unsuccessful', or 'indeterminate'.

The primary parameters of efficacy in this study are time to defervescence and time to negative blood cultures.

Safety analysis included tabulation of type, frequency, duration, and drug relationship of adverse effects as well as changes in patient parameters, particularly those related to the central nervous system. Laboratory parameters pre-dosing and post-treatment were reviewed for changes, particularly those related to renal, hepatic, and hematopoietic functions.

Comment:

1. The wording of how the safety analysis is to be performed is quite vague. An attempt will be made by the reviewer to compare each patient's laboratory data pre- and post-exposure to study drug. All treatment-emergent signs and symptoms will be carefully reviewed.

XIII. Study Evaluation and Results

Study D84-052-02 was performed by Dr. Eduardo Rodriguez-Noriega, MD, at the Infectious Disease Service, Civil Hospital, Guadalajara, Mexico. Enrollment began on 10 June 1985, and was completed on 29 May 1987. A total of 37 adults, 22 males and 15 females, were enrolled. Eighteen patients randomized to the ciprofloxacin arm, and 19 to the chloramphenicol arm. The demographics of the patients who were considered evaluable by the sponsor are shown in the following table:

TABLE 1 DEMOGRAPHICS
PROTOCOL D84-052-02
EVALUABLE PATIENTS PER SPONSOR

Characteristic	Ciprofloxacin	Chloramphenicol
Total enrolled	18	19
Number evaluable	14	15
Mean age (yrs)	29.2	26.7
range	18-45	18-48
Sex (M/F)	9/5	8/7
Mean weight (kg)	59.8	58.5
range	48.5-88.0	47.0-68.0

Evaluability status, as determined by the sponsor, is as shown in Table 2 (next page), and schematically in Attachment 2:

TABLE 2 EVALUABILITY STATUS
PROTOCOL D84-052-02
PER SPONSOR

Characteristic	Ciprofloxacin	Chloramphenicol
Total enrolled	18	19
Evaluable for efficacy per sponsor	14	15
Reasons for nonevaluability:		
Concomitant antibiotics	1	0
No pre-therapy isolate	1	3
No during-therapy cultures obtained	1	0
No post-therapy cultures obtained	1	1

Comment:

1. If the sponsor is held strictly to the definitions used in the protocol, these numbers change substantially. For example, only three of the chloramphenicol patients, and one of the ciprofloxacin patients, had BOTH a positive blood or bone marrow culture within 48 hours prior to the start of therapy AND had blood cultures drawn after the completion of therapy. If one accepts ANY positive pre-therapy culture (blood or bone marrow) as adequate, but still requires a documented blood culture off therapy, these numbers become chloramphenicol four, and ciprofloxacin three.

2. The manner in which patients were deemed nonevaluable because of 'no pre-therapy isolate' appeared to be somewhat arbitrary. In addition to the four patients listed above, there were three other chloramphenicol patients with pre-therapy isolates at day -3 (i.e., three days prior to initiation of therapy) who were considered evaluable; and there were six ciprofloxacin patients with pre-therapy isolates at day -3 (or earlier) who were also considered evaluable. The three chloramphenicol patients excluded by the sponsor for this reason had positive isolates at days -3, -5, and +3; the one ciprofloxacin patient excluded by the sponsor for this reason had a positive culture at day -8.

*3. Although 11/18 ciprofloxacin patients and 10/19 chloramphenicol patients are listed as "bacteriologic eradication" at two [sic] month follow-up in the summary table (Data Listing 12, Vol 8, p 253), there are no such late follow-up cultures listed in the bacteriology section (Data Listing 10, Vol 8, p 219-235). **Because of this, it is difficult to establish whether late bacteriologic follow-up was obtained at all.***

4. The clinical follow-up is stated to be at two weeks post-therapy, but the heading for the 'bacteriologic evaluation' column in Data Listing 12 is labeled 'two months post-therapy'. The CRF does not have space for a 2 month follow-up visit, there is no such follow-up mentioned in the study summary, nor is there any reported clinical follow-up at two months. Thus, this will be assumed to be an error in constructing this table.

For the purposes of this review, the following evaluability criteria will be used:

Clinically evaluable patients must have the following:

1. Signs and symptoms consistent with typhoid fever.
2. Blood or bone marrow culture positive for *S. typhi* or *S. paratyphi* within seven days prior to initiation of therapy.
3. Serial clinical evaluations during and at completion of therapy.
4. No concomitant antibiotics, and
5. A two-week follow-up evaluation.

Microbiologically evaluable patients must have the following:

1) Signs and symptoms consistent with typhoid fever.
2) Documented *S. typhi* or *S. paratyphi* blood or bone marrow infection within seven days prior to initiation of therapy;
3) Documented serial blood cultures obtained following the initiation of therapy, to document clearance of the infecting organism; and
4) If considered a microbiologic cure at the end of therapy, a documented stool culture at two weeks post-therapy follow-up.

Assessment of evaluability is presented in the following table, and schematically in Attachment 3:

TABLE 3 EVALUABILITY PER M.O.
PROTOCOL D84-052-02

Characteristic	Ciprofloxacin	Chloramphenicol
Total enrolled	18	19
Clinically evaluable per reviewer	17	19
Reasons for clinical nonevaluability:		
No pre-therapy isolate	0	0
Concomitant antibiotics	1*	0
Lost to follow-up	0	0
Clinically and Bacteriologically evaluable per reviewer	12	11
Reasons for bacteriologic nonevaluability:		
No during Rx cultures	1	0
Concomitant antibiotics	1*	0
Lost to follow-up	4	7
No pre-Rx culture +	0	1

* Patient #13, listed as 'concomitant antibiotics' by the sponsor. No specific listing of the offending agent is given (Data Listing 6, Vol 8 p 203, entitled "Concomitant Antimicrobial Therapy", states "there were no records for this listing". CFR's were not included in the submission. This patient had no further positive cultures after initiation of ciprofloxacin, so could not be construed as a bacteriologic failure.

Comment:
There is a discrepancy in this table, which is reflective of a discrepancy in the sponsor's data. For the clinical evaluation as shown above, there are no patients lost to follow-up; in the bacteriologic evaluation, however, there are 4 ciprofloxacin and 7 chloramphenicol patients who are listed as lost to follow-up. This reflects the data as presented in the sponsor's tables (Data Listing 12 (page 08-02-0253), Bacteriologic Evaluation, and Data Listing 13 (page 08-02-0259), Clinical Evaluation. Data Listing 12 has several patients with nothing entered in the 'response at 2 month follow-up' column; these patients are presumed to be lost to follow-up. These same patients are listed in Data Listing 13 as 'complete recovery' under the 'Clinical Response at 2 week follow-up' column.

Clinical efficacy.

'Cure' is the resolution of the signs and symptoms associated with a disease.

A cured patient should have resolution of all symptoms and signs upon which the clinical diagnosis of typhoid fever was based. For the purposes of this review, a **clinical failure** will be regarded as the **persistence of any sign or symptom which was considered to be related to the diagnosis of typhoid fever for greater than five days** following the initiation of therapy.

TABLE 4 CLINICAL EFFICACY
PROTOCOL D84-052-02

Characteristic	Ciprofloxacin	Chloramphenicol
Number enrolled	18	19
Clinical severity at entry		
mild	2	0
moderate	9	13
severe	7	6
Number evaluable per sponsor	14	15
Number clinically resolved per sponsor (%)	13 (93%)	15 (100%)
Mean time to last febrile episode (days)	3.6	3.8
standard deviation	1.3	2.1
range	2-6	1-8
Number clinically evaluable per reviewer	17	19
Number clinically cured per reviewer	14 (82%)	14 (74%)
Number clinically failed per reviewer	3 (18%)	5 (26%)
early	3 (18%)	4 (21%)
late	0	1 (5%)
Number receiving concomitant steroids	0	0
Number with previous antimicrobial therapy	7 (38%)	5 (26%)

* Normal range defined as 5,000-10,000 cells/mm^3

Comment:

1. The mean time to last febrile episode is based on the 13 and 15 patients that were considered clinically resolved by the sponsor in the ciprofloxacin and chloramphenicol arms, respectively. Because this reflects the sponsor's evaluation, patients are included who had duration of fever as long as eight days after

initiation of therapy. (Patients with persistent fever longer than five days after initiation of therapy were considered clinical failures by the reviewer.)

2. Early clinical failures were patients who had prolonged fever greater than five days after initiation of therapy. The one late failure, patient #17 in the chloramphenicol arm, is listed by the sponsor as "other" under 'clinical response at two week follow-up' (Data Listing 13, page 08-02-0262); therefore, in the absence of any other information, this patient is considered to be a late clinical failure.

3. The seven ciprofloxacin patients that had previously received antimicrobials included four who had received ampicillin, two each received penicillin and trimethoprim/sulfamethoxazole, and one, metronidazole (several had received more than one previous therapy). Among the chloramphenicol patients, two each had received prior ampicillin and/or penicillin, and one patient each tetracycline, gentamicin, and fosfonomycin (again, several of these patients had received more than one previous antimicrobial).

4. The proposed IDSA Guidelines also mention time to normalization of WBC count (along with time to defervescence) as a secondary clinical response marker. Unfortunately, an inadequate number of WBC data points were collected on the patients in this study. Patients had an entry CBC, usually one CBC at some point during therapy, and a final CBC at or after the completion of therapy. Thus, the average number of days to normalization of the WBC count for the two study arms cannot be meaningfully calculated.

The data pertaining to clinical efficacy are presented in Table 4 (above), as well as schematically in Attachments 2 and 4.

Bacteriologic Outcome

The results of the reviewer's evaluation of bacteriologic outcome is presented in Table 5 (next page), and schematically in Attachment 5. The following definitions are used:

Early failure: the patient's last blood culture, when being called a clinical failure, was still positive.

Late failure: the patient was found to have recurrence (in either stool or blood) with the same organism at the time of late follow-up.

Presumed eradication: the patient, at the time of follow-up, was clinically cured, but no bacteriologic studies were obtained to confirm this.

Documented eradication: the patient had bacteriologic studies (either blood or stool cultures) obtained at the time of late follow-up, which support the clinical findings of cure.

Comment:

Please note that ALL of the bacteriologic isolates in this study were speciated as Salmonella typhi. There were no isolates of S. paratyphi among the 37 patients enrolled in this study.

BACTERIOLOGIC OUTCOME
STUDY D84-052-02
PER MEDICAL OFFICER

Characteristic	Ciprofloxacin	Chloramphenicol
Total enrolled	18	19
Clinically evaluable per reviewer	17	19
Bacteriologically evaluable per reviewer	12	11
Reasons for bacteriologic nonevaluability:		
Concomitant antibiotics	1	0
Lost to follow-up	4	7
No during-Rx cultures	1	0
No pre-Rx culture +	0	1
Bacteriologic outcome:		
Presumed eradication	10 (83%)	10 (91%)
Documented eradication	0	0
Early failure	2 (17%)	1 (9%)
Average time to negative blood culture (days)	6.3	4.6
Number with positive stool cultures	1/18	0/19
Duration of antimicrobial therapy (days):		
Average for clinically evaluable patients (range)	10.9 (8-14)	11.3 (10-14)
Average for clinically and bacteriologically evaluable patients (range)	9.8 (3-14)	10.4 (8-15)

Comment:

1. The difference in rate of clearance of bacteremia is difficult to interpret due to the small numbers. These numbers are crude averages of the number of days, post-initiation of therapy, to the first documented negative blood culture. Since cultures were not obtained every day, these numbers must be viewed cautiously. However, this was a blinded study, and the clinical impressions leading to the decision to obtain blood cultures should have been similar for both arms. These data can be presented in a different manner: three ciprofloxacin patients had positive blood cultures post-initiation of therapy, on days 3, 5, and 7; and four chloramphenicol patients had positive post-initiation blood cultures, on days 1 (3 patients) and 5 (one patient).

2. The paucity of positive stool cultures is surprising, since nearly all of them were obtained during the acute illness or its resolution. Somewhere between one-third and two-thirds of patients would be expected to have positive stool cultures during the second through fourth weeks of illness (Mandell, Principles and Practice of Infectious Diseases, 3rd edition, page 1708).

3. To document intestinal eradication, stool cultures must be obtained after fecal concentrations of the antimicrobial have fallen to undetectable levels; this period is generally recognized to be at least four days following discontinuation of therapy. (In non-typhoidal salmonellosis, administration of antimicrobials is recognized to actually prolong the fecal excretion of the organism.) Thus, collection of appropriate follow-up stool cultures was an important aspect of this study which was not achieved. The latest documented follow-up stool cultures in the two arms of this study were day 7 post-therapy in two, and day 4 post-therapy in one ciprofloxacin patient, and day 2 post-therapy in two chloramphenicol patients.

Bacteriologic sensitivities were performed using the Kirby-Bauer disc technique. (The protocol calls for tube dilution MIC data as well, but none are presented.) Breakpoints employed were as follows:

TABLE 6 ANTIMICROBIAL BREAKPOINTS

Antimicrobial	Disc content	Breakpoints in millimeters		
		Susceptible	Intermediate	Resistant
Ciprofloxacin	5 µg	≥ 18	12-17	≤ 11
Chloro	30 µg	≥18	13-17	≤ 12

By these criteria, all of the isolates were sensitive to ciprofloxacin, and all but one were sensitive to chloramphenicol. One isolate (patient #10) was intermediately sensitive to chloramphenicol, with a zone size of 17 mm. The average of all the zone sizes for all the isolates vs. ciprofloxacin was 26.0 mm (range 21-30 mm); the average and range for chloramphenicol was 19.5 mm (17-21 mm).

Comment:

1. These breakpoints are different from those used in the next study (D87-054), and are different from the current ciprofloxacin labeling and NCCLS recommendations Current susceptibility breakpoints are: susceptible, 21 mm or greater; intermediate, 16-20 mm; and resistant, 15 mm or less. Since the lowest zone size recorded in this study vs. ciprofloxacin was 21 mm, these discrepancies are unlikely to have changed the interpretation of the disc susceptibility tests.

2. Although crude, these averages reflect the fact that the zone sizes for chloramphenicol were closer to the intermediate breakpoint than the zone sizes for ciprofloxacin. Nonetheless, all isolates (except one) were sensitive to both antimicrobials by Kirby-Bauer methodology. Even though multiresistant S. typhi has been a problem in Guadalajara in the past, such isolates were not encountered in this study.

3. The one isolate that was intermediately sensitive to chloramphenicol was from a patient who had randomized to the ciprofloxacin arm. Interestingly, this patient (#10) was the one patient who had the longest persistence of culture positivity, with blood cultures remaining positive at day 7 of therapy. These sensitivity results should have been available to the investigator within the first three days of therapy. If the blinding of this study remained intact, then this would suggest that the investigator kept the patient on study, with the possibility that inadequate therapy with chloramphenicol was being given. The patient's clinical course apparently was improving, despite the persistence of positive blood cultures. This patient was eventually cleared of his infection,

and was called a 'late and complete' eradication by the sponsor. This patient was reported as 'eradicated at follow-up' at the time of the two week post-therapy visit.
4. There did not appear to be any problem with development of ciprofloxacin resistance while on therapy, which can be seen when using ciprofloxacin for the treatment of Gram-negative organisms such as Pseudomonas aeruginosa. The zone sizes of the repeated isolates in patient #10 remained stable over seven days of exposure to ciprofloxacin, as well as for patient #29, who had a repeat blood isolate on day 3 of ciprofloxacin therapy. Obviously, there are insufficient data here from which to draw any conclusions concerning the possible development of ciprofloxacin resistance. The scenario in which this phenomenon would require careful observation is in the treatment of the chronic carrier state. Such patients will be exposed to long-term ciprofloxacin therapy, and their Salmonella typhi isolates will be under significant antibiotic pressure which may lead to the in vivo selection of topoisomerase mutants.
5. A poster presentation at the 1992 ICAAC examined trends in ciprofloxacin resistance patterns in the USA (Thornsberry C, Marler JK, Bouchillon S, and Rich T. Bacterial resistance to ciprofloxacin in the US: a national surveillance study, 1990-1991. 1992 ICAAC, abstract #776.) This was a survey of 154,689 isolates from 26 institutions in 21 states. The survey included 1,516 Salmonella isolates, of which 1,224 were Salmonella species (i.e., non-typhoidal strains). There were 30 S. typhi isolates in this survey, and all were sensitive to ciprofloxacin (MIC ≤ 1 µg/mL). The only resistance noted in this survey was in one of the thirty reported strains of S. arizonae (C. Thornsberry, personal communication).

Safety

There were no deaths reported during this study. There were no reported treatment-emergent signs and symptoms in the ciprofloxacin arm, and one report each of nausea and diarrhea in two of the 19 chloramphenicol patients. One of these patients (#15) had 2 days of moderate diarrhea that was considered probably related to chloramphenicol administration; therapy was stopped on day 8, and the symptoms resolved the following day. (The patient was nonetheless clinically cured and a presumed bacteriologic eradication.) The nausea episode (patient #26) was considered mild and probably related to chloramphenicol administration, but did not require discontinuation of therapy. The patient was able to complete 10 days of therapy, and was clinically and bacteriologically cured.

Review of laboratory parameters monitored during the course of therapy revealed insignificant changes in hematologic parameters, equally distributed between the treatment arms. There were no significant changes in renal function or electrolytes in the two groups, with the exception of one chloramphenicol patient who had a BUN rise from 7 mg/dL pre-therapy to 28 mg/dL two days post-therapy (with no other lab abnormalities noted, indicating probable pre-renal azotemia). Liver function studies were elevated at baseline in many patients in both arms of the study; these abnormalities all resolved during treatment or by the time of follow-up. There were four ciprofloxacin patients and one chloramphenicol patient who had single transaminase determinations that were elevated (with no follow-up values to document resolution or progression on therapy). One ciprofloxacin patient had an increase in SGOT from 25 to 44 U/L after 10 days' therapy. Urinalysis revealed one patient (#16) in the ciprofloxacin group who developed crystalluria on therapy; this patient's renal function remained stable.

Comment:

There were no observed events, either TESS or laboratory, that were unusual or unexpected. The one patient with crystalluria during ciprofloxacin administration did have alkaline urine, which is known to predispose to crystal formation.

XIV. CONCLUSIONS REGARDING STUDY D84-052-02

1. This study was relatively sound in its design, but was poorly executed. An inadequate number of bacteriologic studies were performed in the great majority of patients, both during therapy and at the time of follow-up. Optimally, one would obtain test-of-cure blood cultures, ≥ 24 hours AFTER completion of therapy, to document bacteriologic eradication; only three ciprofloxacin and four chloramphenicol patients had any such cultures obtained. The longest documented follow-up culture of any sort was at day 7 post-completion of therapy, and these were stool cultures in two chloramphenicol patients.

2. The original protocol calls for 100 evaluable patients to be enrolled in this study; enrollment was apparently halted after 37 patients had been entered. There is no explanation given for this. The small number of enrolled patients in each arm weakens the power of this study considerably.

3. Given the serious shortcomings noted, ciprofloxacin and chloramphenicol appeared to be equally efficacious, although, due to small numbers, no statistically valid conclusions can be reached from this study. Bacteriologic failures, defined as persistence of positive blood cultures at the time of clinical failure (five days post-inititation of therapy), were 2/12 (17%) in the ciprofloxacin arm, and 1/11 (9%) in the chloramphenicol arm. Clinical resolution of signs and symptoms was similarly prompt in both treatment groups, although chloramphenicol may have cleared the blood of organisms more rapidly.

4. The dosage of ciprofloxacin used in this study was 750 mg q12h which is higher than the proposed dosage (500 mg q12h for 10 days). Thus, this study cannot be considered directly supportive of the proposed labeling.

5. The ability to evaluate the safety profile of either of these drugs was hampered by the small numbers of patients and the somewhat incomplete nature of laboratory safety data collection. Also, the CRF for the chloramphenicol patient who was discontinued due to diarrhea could not be located for review. Based on the data submitted to the FDA for review, there did not appear to be any major safety concerns raised by this study.

STUDY #D87-054: A comparative, double-blind efficacy and safety study of ciprofloxacin with chloramphenicol in the treatment of typhoid fever.

I. Study Design

This study was similar in design to the previously reviewed study conducted in Guadalajara, Mexico, by Dr. Rodriguez-Noriega (#D84-052-02). Please refer to the synopsis of study design, beginning on page 8 of this review, for further information. The aspects of this study design which differ from D84-052-02 are as follows:

1. Minimal enrollment age is 16 rather than 18 years old.

2. Patients older than 60 years of age are excluded.

3. Pregnancy is listed as an exclusionary criterion.

Comment:
There is no specific mention in the protocol concerning how pregnancy status was determined (i.e., was a urinary β-HCG done on all females at entry?).

4. **The dosage of ciprofloxacin used is 500 mg q12h for 10 days.**

Comment:
The previous study dosed ciprofloxacin at 750 mg q12h. This dosage (500 mg q12h x 10 days) is the regimen submitted in the proposed labeling.

5. Specimens of bile were to be obtained pre-therapy and at day 7 of therapy via the string capsule device.

Comment:
The protocol references a 1981 New England Journal of Medicine letter in which the investigator described the utility of this procedure in improving the bacteriologic diagnosis of typhoid fever (NEJM 304: 54, 1981). It is important to note that this reviewer will only regard as evaluable those patient with blood or bone marrow-confirmed typhoid fever.

6. The criteria for interpretation of zone sizes for the determination of disc susceptibility to ciprofloxacin are different. This study uses ≥ 21 mm as susceptible (whereas the previous study used a less stringent ≥ 18 mm), 16-20 mm for intermediate (12-17 in the previous study), and ≤ 15 mm for resistant (versus ≤ 11 mm in the previous study). The disc used is the same standard 5 µg disc.

Comment:
This difference will make it less likely that an isolate will be classified as 'sensitive' when it is, in fact, resistant or intermediate. In other words, this difference in breakpoints serves to protect patients from potentially inappropriate therapy. (The breakpoints used for chloramphenicol are the same as used in the previous study, which are the NCCLS standard.)

7. Patients were to be followed up weekly for the first month post-therapy, and biweekly for the second month post-therapy. At two months post-completion of therapy, stool and urine cultures were to be obtained. Appropriate cultures were to be obtained at any point in the follow-up if relapse was suspected.

Comment:

The value of this study will depend in large part on the adequacy of follow-up achieved, and the numbers of evaluable patients that result. The previous study had only three patients with any documented bacteriologic follow-up more than two days post-completion of therapy.

II. Study Evaluation and Results

Study D87-054 was performed at two different sites. Investigators, locations, and enrollment are shown in the following table:

TABLE 7 INVESTIGATORS AND ENROLLMENT
PROTOCOL D87-054

Investigator and Location	Number enrolled		Number evaluable per sponsor	
	Cipro	Chloro	Cipro	Chloro
(01) Edward Gotuzzo, MD Institute of Tropical Medicine University of Peru Hospital Lima, Peru	52	52	46	48
(02) Jose L. Bran, MD Hopital General San Juan de Dios Guatemala City, Guatemala	60	60	52	52

Sponsor evaluation

Demographics of the evaluable subset, and baseline disease severity parameters (per sponsor) are presented in Table 8: